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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/609,019	COOPER ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 52-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 52-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/20/07; 6/22/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments and claims filed August 3, 2007, has been received and entered.

Claims 1-21 and 52-80 are under examination.

Withdrawn-Claim Objections

The objection to claim 1, 52 and 63 is withdrawn in view of amendments to the claims.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8-10, 15-17 and 52-53, 61-62 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771–776, IDS) and Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000, IDS).

Cooper taught a vector comprising a gene encoding a transposase operably linked to a promoter, Mo transposon insertion sequences recognized by the transposase; and an exogenous gene located between the transposon insertion sequences. The promoter directing expression of the transposase gene may be inducible. See the claims. In column 8, at lines 58-67 Cooper listed transposases, including Tn10 and Tn5, which may be used in combination with the same vector.

The claims require a modified transposase gene, wherein two to ten codons, are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without changing the amino acid encoded by the codon. Cooper et al discussed use of both constitutive and inducible promoters for directing expression of both the transposase gene and the gene of interest. See for example, columns 15-18. Cooper sought to express transgenes in various vertebrates as evidenced by the teachings in column 9, in lines 40-50. Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG or a vector comprising more than one gene of interest operably linked to more than one promoter between the transposase insertion sequences.

It is noted that other transposase vectors were known at the time of filing of this application. Savakis et al use of modified transposon wherein the modification includes removal or disruption of transposase sequences or the incorporation of one or more heterologous coding sequences and/or expression controls sequences (see para. 23 of the published application). Although, Savakis et al exemplified type-2 transposon such as Minos to generate transgenic animal, however, he generally embraced the idea of using any natural transposon (see para 22). It is noted that Savakis et al contemplate heterologous to genetic sequences that are from a species other than the organism or transposon of interest (see para. 24 of the published application). Savakis et al disclose variety of promoters that could be used including tissue-specific promoters, and inducible promoters (para 26). It is also noted that Savakis et al also contemplates that the sequence of the transposase may be modified to optimize codon usage and thus, increase transposition frequencies. It is noted that Savakis et al describe that optimization of codon usage by converting less frequently used codons to more frequently used codons is a method well known in the art to increase the expression levels of a given gene (see para. 143). However, Savakis et al differed from claimed invention by not disclosing modified prokaryotic transposase comprising Kozak sequence.

However, at the time the claimed invention was made inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. It was also well known at the time the invention was made that an expression cassette may comprise gene of interest in operable linkage with one or more than one promoter. Prior to instant invention, it was generally known in the art that initiation codon of a prokaryotic gene such as one disclosed by Williamson would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. It is noted that most of the prior art generally teaches that initiation of eukaryotic mRNA translation occur exclusively at AUG Codons (see page 773, col. 1, last para). Williamson teach modifying the 5' end of a prokaryotic gene to include a eukaryotic start codon, the Kozak expression start site consensus sequence to facilitate manipulation of the gene (see abstract and entire article). Williamson et al teach

expression of the prokaryotic gene lysostaphin and processing of the precursor to produce active secreted enzyme in eukaryotic system. However, Williamson differed from claimed invention by not teaching prokaryotic transposase gene that is codon optimized.

Accordingly, in view of the teachings of Cooper, Williamson and Savakis, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Williamson et al specifically indicated that any initiation codon of a prokaryotic gene would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. One of ordinary skill in the art would have been sufficiently motivated to position Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view of disclosure by Williamson. In addition, It is evident that the person of ordinary skill would have optimized the transposase gene, because Savakis et al had already described that transposase may be modified to optimize codon usage to direct expression of different gene of interest in different host with increased transposition frequencies. It is emphasized that changing codon by individually modifying wild type sequence of CG at third base position of the codon to A or T is routine optimization depending upon transgene and host species as per the teaching of Savakis.

One who would practiced the invention would have had reasonable expectation of success because Williamson et al had already described use of Kozak sequence to express transposase gene in eukaryotic system. Williamson et al specifically taught that a Kozak sequence comprising ACCATG is the optimal sequence for initiating translation in vertebrate cells and it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter and further optimize the codon as per the requirement of transgene and host cell as per the teaching of Savakis.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771–776, IDS) and Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000), Hackett et al (US Patent no. 6489458,

dated 12/3/2002, filing date 9/10/1998 IDS), MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS).

The combined teachings of Cooper, Williamson et al and Savakis have been discussed above and are relied upon in same manner here. However, none of the references explicitly teaches advantage of using ovalbumin or other egg directing sequences.

MacArthur et al teach vector comprising the control elements that include an enhanced promoter directing the expression of the transgene in the oviduct, an untranslated region 5' to the structural gene (coding region) of appropriate length and sequence to promote efficient translation, and a signal sequence directing the secretion of the transgene product in the egg white (col.3, lines 1-6).. MacArthur et al teach the promoter may be ovalbumin, lysozyme, conalbumin and ovomucoid promoters and combinations thereof (See col. 7, lines 30-40). MacArthur et al also contemplate that the control sequences include a promoter directing the expression of the transgene in the liver and a signal sequence directing the uptake and secretion of the transgene product into the egg yolk-using promoter such as vitellogenin or combinations thereof (see col. 7, lines 40-45). MacArthur et al disclose control elements, which flank the transgene, include promoters and enhancers that could be used (col. 4, lines 64-65) including tissue-specific promoters. MacArthur et al teach that the vector's 5' untranslated region (UTR) very closely resembles that of ovalbumin RNA with only difference is a one base mutation near the 5' end which was necessary for construction and a 77 base leader is more consistent with Kozak's that is required for maximum translational efficiency. It is noted that MacArthur et al contemplated any UTR with a functional sequence around the start codon could be used for enhancing translational efficiency (See col. 9, lines 1-9). MacArthur et al disclose use of standard stop codons and the polyadenylation signal are included 3' to the structural gene (See col. 9, line 53-55). It is also noted that MacArthur et al emphasize the usefulness of providing gene to an avian or chicken cell, wherein the gene is expressed in the hen's oviduct and secretion of the gene product is in the hen's eggs. However, MacArthur et al do not disclose using ovalbumin or any other promoter with transposon-based vector. Prior to instant invention, use of control elements that included promoters was generally routine in the art. Hackett et al disclose variety of promoters that could be used including constitutive promoters, tissue-specific promoters, and inducible promoters (column 12, lines 35-40) to express transgene. It is also noted that Hackett also contemplates a particular DNA sequence could be modified to employ the codons preferred for a particular cell type. In addition, Hackett et al also disclose different nucleic acid encoding protein including growth hormone and insulin comprising a promoter such as ovalbumin promoter that could direct expression of transgene for the production of recombinant protein in milk, urine, blood or eggs (column 16, lines

20-45). Furthermore, Hackette et al also disclose tagging of an exogenous gene and teach isolating the tagged gene (see example 7 and 8)

However, MacArthur and Hackett et al differed from claimed invention by not disclosing control elements in vector comprising prokaryotic transposase gene.

Accordingly, in view of the teachings of Cooper, Williamson and Savakis, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Williamson et al specifically indicated that any initiation codon of a prokaryotic gene would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. One of ordinary skill in the art would have been sufficiently motivated to position Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view of disclosure by Williamson (supra). Furthermore, Savakis et al provided motivation to modify the wild type transposase gene to optimize codon usage to direct expression of different gene of interest in different host with increased transposition frequencies. It is emphasized that changing codon by individually modifying wild type sequence of C or G at third base position of the codon to A or T is routine optimization depending upon transgene and host species as per the teaching of Savakis. The person of ordinary skill would be further motivated to modify the vector by including control elements including a signal sequence and using promoter such as ovalbumin, lysozyme, conalbumin and ovomucoid s (supra) as per the teaching of MacArthur and Hackett to express gene in milk or egg.

One who would practiced the invention would have had reasonable expectation of success because MacArthur/ Hackett had already described that signal sequence and promoters that could be used to direct expression of the transgene in milk or egg. Williamson and Savakis had already described use of Kozak sequence to express transposase gene in eukaryotic system and optimization of codon usage depending of cell and transgene. Thus, it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter such as ovalbumin to direct expression of the gene in egg or milk.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-21, 52-74, 76, 78 and 79 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771–776, IDS) and Savakis et al (US Patent

application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000, IDS), Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998, IDS) or MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS) and further in view of Wallace, R. A, King J.L and Sanders, G.P., (Biology: The Science of Life, 1986, Scott Foresman and Company, pp 235, IDS).

The combined teachings of Cooper, Williamson et al, Savakis and MacArthur /Hackett have been discussed above and are relied upon in same manner here. However, none of the references explicitly teaches using two-stop codon with Poly A.

Prior to filing of this application, Wallace et al teach three stop codons UAA, UAG and UGA that are used as stop codon. It is noted that Wallace et al also disclose double stop codon such as UAA-UAG to ensure message to ribosome (pp 235, col. 2, see section) polypeptide chain termination.

Accordingly, it would have been obvious and within the scope of skill for an artisan to subject the vector taught by Cooper, Williamson, Savakis and MacArthur /Hackett to include two-stop codon operably linked to the transposase as taught by Wallace. MacArthur et al had already taught use of standard stop codons and the polyadenylation signal. One of ordinary skill in the art would have been motivated to include multiple-stop codon to ensure proper termination of transposase synthesis and would have also included poly A as a obvious modification for expression in mammalian system. It is emphasized that a conalbumin Poly A broadly encompasses Poly A or any signal and does not require entire non-coding region of a conalbumin for instant rejection.

One who would practiced the invention would have had reasonable expectation of success because Wallace had already described use of two stop codon to ensure polypeptide chain termination. It would have only required routine experimentation to modify the vector to include two stop codons operably linked to the gene to enhance the termination of transposase synthesis.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Response to Arguments

Cooper, Williamson et al and Savakis

Applicant's arguments with respect to claims 1-6, 8-10, 15-17 and 52-53, 61-62 has been fully considered but they are not persuasive. Applicants assert that the cited references do not describe each and every element of the claimed invention.

Also, the cited references do not, alone or in combination, provide a motivation or suggestion to combine the references, or a reasonable expectation that such a combination would be successful for the reasons below. Applicants argue the optimization of codon usage that is described by Savakis et al. is distinct from Applicants" modification of the N-terminal first 10 codons to replace C or G at the wobble position with A or T. Applicants are not modifying the transposase to optimize codon usage for a particular host, but to increase strand dissociation during transcription. Applicants also assert that the although Williamson et al describes use of a Kozak sequence to promote the initiation of translation in a eukaryotic system, Williamson also states that "the lysostaphin gene joins a small group of prokaryotic genes which are known to be expressed in mammalian cells (Williamson et al. at page 775, col. 2)

It appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention of a vector comprising a prokaryotic gene and claimed embodiments of modified prokaryotic transposase gene. It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art is important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It also appears that applicant is attempting to attack each reference individually. However, in a 103 rejection the references must be considered as a whole.

In the instant case, independent claim 1 requires 3 basic elements in prior art 1) a prokaryotic transposase gene operably linked to a promoter wherein 2) the 3' end of the promoter comprises a Kozak sequence to include first codon of the transposase gene and wherein 3) transposase gene is modified such that plurality of codon of the transposase gene that encodes amino acid 2-10 are modified from C or T to A or T at third position of the codon without changing the amino acid encoded

by the modified codon. Cooper et al disclose the vector comprising a gene encoding a transposase operably linked to a promoter, Mo transposon insertion sequences recognized by the transposase; and an exogenous gene located between the transposon insertion sequences. The promoter directing expression of the transposase gene may be inducible. See the claims. In column 8, at lines 58-67 Cooper listed transposases, including Tn10 and Tn5, which may be used in combination with the same vector. Cooper et al discussed use of both constitutive and inducible promoters for directing expression of both the transposase gene and the gene of interest. See for example, columns 15-18. Cooper sought to express transgenes in various vertebrates as evidenced by the teachings in column 9, in lines 40-50. Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG or a vector comprising more than one gene of interest operably linked to more than one promoter between the transposase insertion sequences. The claims also require a modified transposase gene, wherein two to ten codons, are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without changing the amino acid encoded by the codon. However, prior to instant invention, Savakis et al disclose variety of promoters that could be used including tissue-specific promoters, and inducible promoters (para 26). It is also noted that Savakis et al also contemplated codon optimization by converting less frequently used codons to more frequently used codons, a method well known in the art to increase the expression levels of a given gene (see para. 143). In addition, prior to instant invention, inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. It was also well known at the time the invention that an expression cassette may comprise gene of interest in operable linkage with one or more than one promoter. Prior to instant invention, it was generally known in the art that initiation codon of a prokaryotic gene such as one disclosed by Williamson

would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. It is noted that contrary to applicant's assertion, most of the prior art generally teaches that initiation of eukaryotic mRNA translation occur exclusively at AUG Codons and Williamson teach modifying the 5' end of a prokaryotic gene to include a eukaryotic start codon, the Kozak expression start site consensus sequence to facilitate manipulation of the gene (see abstract and entire article, see page 773, col. 1, last para). The reference is included to demonstrate that modification of prokaryotic gene for expression in eukaryotic system required modification of transgene by inclusion of Kozak sequence at transcription initiation site. It is apparent from the preceding analysis that claimed embodiments were known in prior art and one of ordinary skill in the would have studied Cooper, Williamson and Savakis to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Williamson et al specifically indicated that any initiation codon of a prokaryotic gene would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. In addition, use of Kozak sequence to initiate transcription of a transgene was known to one of ordinary skill in the art. It is emphasized that contrary to applicant's argument based on the teaching of codon optimization, one of ordinary skill in the art would be aware that any organism that has a relatively low G+C content of will be less likely to have a G or C at the third position of a codon (wobble position) than a Adenine or Thymine to specify an amino acid that can be represented by more than one codon. In addition, nucleotide substitution that does not alter the amino acid sequence of an encoded protein due to the degeneracy of the genetic code that usually involved the third base (wobble position) of codons was also known as routine optimization to obtain optimal expression. One of ordinary skill in the art would have been sufficiently aware of these routine codon optimization processes

and would have positioned Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view of disclosure by Williamson. In addition, It is evident that the person of ordinary skill would have optimized the transposase gene to direct expression of different gene of interest by individually modifying wild type sequence of CG at third base position of the codon to A or T. It is emphasized that modifying plurality of first few codon and not the entire gene is also within the skills of one of ordinary skill in the art and it would be obvious to artisan that modifying first few codon would result in increased transcription. With respect to applicant's argument that Cooper et al teaches away from the applicant's vector. Applicants assert that Cooper et al teaches a transposase based vector comprising unmodified gene and one skill in the art reading Cooper would not be motivated to incorporate Kozak sequence (see page 13 of the arguments). It is emphasized that the Cooper et al exemplified a vector comprising prokaryotic transposase gene that could be used to transfect eukaryotic system. Cooper et al specifically taught transposase that contained mutations that make it less specific for preferred insertion sites and thus increases the rate of transgene insertion. Cooper et al also emphasize the long felt need in transgenic avian art for safe and effective vector for transgenesis particularly since it was known that previously used vectors have low efficiencies in avians wherein construct often integrate in avian species at low frequencies. Given the art recognized need for improving the efficacy of known vector, contrary to applicant's argument it would have been obvious for one of ordinary skill in the art to use a transposon based vector disclosed by Cooper to further modify by inclusion of Kozak sequence and modify the first few codons of the prokaryotic transposase gene to efficiently express transgene in bird that usually showed low integration frequencies. In addition, it is noted that recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at

20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant case, references of Cooper provided adequate guidance with respect to known transposon based vector comprising transposase gene operably linked to promoter that would have been obvious to one of ordinary skill in the art to combine with disclosure of Williamson in order to improve the efficacy of the vector with reasonable degree of predictability. In addition, optimization of plurality of codon is routine optimization in the art and one of ordinary skill in the art would be aware of nucleotide substitution that does not alter the amino acid sequence of an encoded protein due to the degeneracy of the genetic code that usually involved the third base (wobble position) of codons and it would have been *prima facie* obvious for the artisan to try to do such modification in order to improve the transcription resulting in enhanced expression of transgene in chicken or any other host species with reasonable degree of predictability.

Cooper, Williamson and Savakis, Hackett et al, MacArthur.

Applicant's arguments with respect to claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79 have been fully considered but they are not fully persuasive. Applicants assert that the cited references do not describe each and every element of the claimed invention. Applicants also argue that neither Hackett et al, nor MacArthur teach prokaryotic transposase rather they describe different vector system.

In response, Applicant' s attention is directed to a well-established case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art is important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It also appears that applicant is again attempting to attack each reference individually. However, in a 103 rejection the references must be considered as a whole. In the instant case, both the references are included to merely demonstrate that regulatory control elements were known in prior art that included an enhanced promoter directing the expression of the transgene in the oviduct, an untranslated region 5' to the structural gene (coding region) of appropriate length and sequence to promote efficient translation, and a signal sequence directing the secretion of the transgene product in the egg white (col.3, lines 1-6). In addition, MacArthur et al teach the promoter may be ovalbumin, lysozyme, conalbumin and ovomucoid promoters and combinations thereof (See col. 7, lines 30-40), while Hackett provided guidance with respect to ovalbumin promoter that could direct expression of transgene for the production of recombinant protein in eggs. Given that tissue specific promoters were known in prior art, it would have been prima facie obvious to one of ordinary skill in the art to modify the vector disclosed by Cooper, Williamson and Savakis to include a signal sequence and using promoter such as ovalbumin, lysozyme, conalbumin and ovomucoid as per the teaching of Macarthur and Hackett to express gene in egg.

With respect to applicant's argument that there is no expectation of success in designing the SB transposase system, it is noted that cited references do not teach modifying the SB transposases system. In fact, combination of reference teaches modifying a vector comprising prokaryotic transposase gene (see Cooper et al) which is optimized to more efficiently work in eukaryotic system (see discussion

in previous section). The references of MacArthur and Hackett are included to demonstrate that regulatory sequence that direct the expression of transgene in specifically in avian egg were known in prior art and it would be obvious for one of ordinary skill in the art to use available regulatory sequence to express transgene under control of promoter and signal sequence disclosed by MacArthur and Hackett.

Cooper, Williamson and Savakis Hackett or MacArthur and Wallace

Applicant's arguments with respect to claims 1-21, 52-74, 76, 78 and 79 have been fully considered but they are not fully persuasive. Applicants assert that the cited references do not describe each and every element of the claimed invention as there is no teaching to include poly A sequence that is operably linked to prokaryotic gene. . Applicants also argue that since most of the prokaryotic gene do not include poly A sequence, there is no expectation of success that a poly A sequence could be operably linked to prokaryotic transpose gene (see page 17 and 18).

The discussion in preceding section describes the modified transposase gene for increased transcription in eukaryotic system. One of ordinary skill in the art is aware of role of double stop codon to ensure message to ribosome polypeptide chain termination as per the teaching o Wallace. Although, MacArthur et al did not teachuse of polyA with prokaryotic transposase gene, but he taught the significance of using stop codons and the polyadenylation signal to ensure proper termination of transposase synthesis. Based on the teaching of Macarthur et al and general skill in the art, one of ordinary skill in the art would be aware of need of terminating transposase synthesis by using stop codons, particularly since combination of references teach modified transposon based vector that is modified to include Kozak sequence and individually modifying codon 2-10 of the wild type sequence of CG at third base position of the codon to A or T of the prokaryotic transposase gene to efficiently express transgene in eukaryotic system. It would be obvious for one of

ordinary skill in the art to try to further optimize the poly A sequence to be included in the modified transposon based vector as a obvious modification for expression in eukaryotic system. Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Secondary considerations:

With respect to applicant's argument of unexpected result, it is noted Examiner would agree that cited reference of Cooper and other existing vector for avian transgenesis had poor integration frequency and it was art recognized goal to improve the efficiency of the vector. Examiner has cited references to show it would have been prima facie obvious for one of ordinary skill in the art to include Kozak sequence and individually modify plurality of first few codons codon 2-10 of the wild type sequence of CG at third base position of the codon to A or T since it is generally known that any organism that has a relatively low G+C content of will be less likely to have a G or C at the third position of a codon (wobble position) than a Adenine or Thymine to specify an amino acid that can be represented by more than one codon. In addition, nucleotide substitution that does not alter the amino acid sequence of an encoded protein due to the degeneracy of the genetic code that usually involved the third base (wobble position) of codons was also known as routine optimization to obtain optimal expression. The declaration filed m Sept. 26, 2006 shows the use of a vector (pTN mod)with a monoclonal antibody encoded by the gene of interest resulted in very high efficiency. Furthermore, applicants also assert that instant vector enables vectors to transfect cells in a live animal to produce chimeric animal. In response, it is noted that exemplified vector in the Declaration uses a specific modification, promoter and regulatory control sequence which is different from one broadly recited in the independent claims. In absence of any specific embodiments, it would have been obvious for one of ordinary skill in the art to try to optimize the existing transposon vector comprising prokaryotic gene to increase its efficiency in

eukaryotic system. Additionally, see MPEP §716.02(d) which states, "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." The claims are not commensurate in scope with that which Applicants argue is unexpected.

Conclusion

No claims allowed.

The following art made of record and not relied upon is considered pertinent to applicant's disclosure: Herrero et al (Journal of Bacteriology, 1990, 6557-6567, IDS).

Zhang e al (WO 01/83786, dated 11/8/2001)

Schulz (journal of Mol. Biol. , 1991, 221, 65-80)

Claims 75 and 80 are free of prior art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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